Remarks

Reconsideration of this Application is respectfully requested.

Claims 36, 37, 40, 41, 43, 44, 46-49, 58 and 59 are pending in the application, with claim 36 being the sole independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 36, 37, 40, 41, 43, 44, 46-49 and 58 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See* Office Action dated March 14, 2005, page 2. Applicants respectfully traverse this rejection.

The written description rejection is based on the Examiner's position that the claims "are directed toward a genus of methods for identifying separin inhibitors using *any substrate.*" *See* Office Action dated July 23, 2004, page 2 (emphasis added). According to the Examiner:

> Although the specification lists several separin substrates in addition to SEQ ID NO: 1, the specification, however, does not

> describe a substantial portion of an amino acid sequence that is common to all members of the claimed genus of separain [sic: separin] substrates. The claims encompass a highly variant genus of substrates with widely differing structural, chemical, and physical characteristics. The genus is highly variable because a significant number of structural differences between genus members exists.

See Office Action dated March 14, 2005, page 2. Applicants respectfully disagree with this assertion.

The present claims are directed to methods that include incubating with a test compound a separin in the presence of a separin substrate. The claims specify that the separin substrate is a peptide or polypeptide comprising an amino acid sequence EXXR, wherein X is any amino acid, and the substrate is capable of being cleaved by the separin. The claim therefore includes both a structural and a functional definition of the separin substrate. The specification provides more than adequate description of the genus of separin substrates included in the practice of the claimed methods.

The written description requirement for a genus can be satisfied through, *e.g.*, sufficient description of a representative number of species by actual reduction to practice. *See* M.P.E.P. § 2163 (citing *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997)). What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. *See id.*

The present specification sets forth numerous separin substrates that can be used in the practice of the claimed methods, including, *e.g.*, *S. cerevisiae* Scc1 and Rec8, *S. pombe* Rad21, and human SCC1, and several variants thereof. *See* Applicants' previous response (filed December 20, 2004) at pages 8-9. Importantly, working examples are presented that illustrate cleavage of the following separin substrates:

(i) yeast Scc1 tagged with HA epitopes (Examples 2 and 3 (pages 34-35));

(ii) purified yeast Scc1 (Example 5 (pages 36-37));

(iii) untagged human SCC1 (Example 9 (page 38)); and

(iv) human SCC1 tagged with Myc epitopes (Examples 10-13, pages 38-40)).

The specification clearly contemplates the use of numerous separin substrates in addition to those used in the working examples. For instance, the specification notes that the *S. pombe* protein Rad21, and Rad21 derived sequences, can be used as separin substrates. *See* specification at page 18, lines 10-13 ("the S. pombe homologue of Scc1 (called Rad21) contains two sequences which are similar to the two known cleavage sites in Scc1, and Rad21 derived sequences may therefore be used to generate a substrate for S. pombe Esp1 (called Cut1).") The specification further sets out various methods that can be employed to identify a wide variety of separin substrates for use in the practice of the claimed methods. For example, it is noted in the specification that:

> Based on information about the sequence specificity of the separin proteolytic cleavage site in yeast and in man, *other potential substrates for the protease can be found in other organisms*,

> including humans, which also allows for the design of peptides derived from these substrates, which are useful as substrates in the screening assay of the invention.

See specification at page 19, lines 21-25 (emphasis added). The specification also sets out methods that can be used to identify variants of known separin substrates and additional substrates. According to the specification:

> In a preferred embodiment, the substrate is a peptide containing the cleavage site of the naturally occurring substrate. The sequence specificity of the proteolytic cleavage can be determined by testing a variety of different peptides. The peptide may be of natural origin, i.e. derived from the natural SCC1, or a variant. An example for a natural peptide [is] the human SCC1 peptide as set forth [in] SEQ ID NO:1, or a fragment thereof that contains the separin cleavage site. Variants can be generated either by synthesising variant peptides or by mutating DNA sequence from genes encoding cohesion proteins. More specifically, other substrates for separin can be identified by searching for small DNA fragments from the yeast genome or an oligonucleotide library that can replace the normal Scc1 cleavage sites. Oligonucleotides may be inserted into a SCC1 gene (lacking both natural cleavage sites) under control of the GAL promoter on centromeric pla[s]mid. Yeast cells may be transformed with a library of such constructs and only plasmids whose modified Scc1

> protein can be cleaved by the separin activity will permit growth in the presence of galactose. The peptides encoded by the positive constructs are useful as substrates for separin in the screening assay of the invention.

See specification at page 19, line 26, through page 20, line 12. This method would allow persons of ordinary skill in the art to identify a multitude of separin substrates that can be used in the practice of the claimed methods.

The specification additionally notes that human SCC1 is cleaved at the EXXR motif, "which is conserved in many SCC1 homologs in different species and is also found in both N-terminal cleavage sites of budding yeast Scc1." *See* specification at page 15, lines 10-13. It is clear from the foregoing that the specification contemplates the use of any separin substrate for use in the screening methods of the invention, in particular all separin substrates having the sequence EXXR.

The level of skill and knowledge in the art relating to the production and use of proteolytic substrates was extremely high at the time of the effective filing date of the present application. With knowledge of a particular cleavage motif (such as EXXR), a skilled person would simply identify and/or isolate naturally occurring peptides or polypeptides having the cleavage motif, or alternatively, produce synthetic peptides that contain the motif. The isolation of naturally occurring peptides or polypeptides having a particular cleavage motif could have easily been accomplished using, *e.g.*, genetic screening methods. *See, e.g.*, specification at page 20, lines 1-12 (describing exemplary screening

methods that could have easily been used to identify additional separin substrates and variants thereof).

The level of skill in the art of producing synthetic proteolytic substrates containing a particular cleavage motif was likewise extremely high. For example, at the time of the effective filing date of the present application, techniques for producing *thousands* of peptides having predetermined amino acid sequences were routine in the art. Such techniques include, *e.g.*, the production of recombinant nucleic acid molecules that encode peptides containing a protease cleavage motif, and the direct production of multiple peptides that include the cleavage motif (*see, e.g.*, Rodda, "Synthesis of Multiple Peptides on Plastic Pins," in *Current Protocols in Protein Science*, John Wiley & Sons, Inc. (1997), copy submitted herewith as Exhibit 1). As noted by Rodda, "The key to preparing large numbers (hundreds to thousands) of synthetic peptides in a short time and at minimal cost is to use a parallel synthesis technique which is efficient and can be done on a small scale." *See* page 18.2.1, first paragraph. Thus, the level of skill in the art of producing multiple peptides and polypeptide sequences, including those containing a particular proteolytic cleavage motif such as EXXR, was very high.

Thus, the specification sets forth several exemplary separin substrates, including working examples that illustrate the use of such substrates. The specification also provides specific methods for easily obtaining additional substrates. In view of this disclosure and the extremely high level of skill in the art relating to the isolation and use of proteolytic substrates, a person of ordinary skill in the art would clearly appreciate that Applicants were

in possession of the genus of separin substrates that are used in the practice of the currently claimed methods.

Moreover, the USPTO's own Written Description Guidelines provide further support for Applicants' position that the genus of separin substrates included in the present claims is more than adequately described. For instance, in Example 14 of the Guidelines (copy submitted herewith as Exhibit 2), the written description requirement is found to be satisfied for a claim directed to "A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→B." As noted in the Example, the specification describes only one species of the genus (*i.e.*, SEQ ID NO: 3). *See* Written Description Guidelines Example 14, page 54. According to the Guidelines:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity.

See id. Thus, the critical factors leading to the conclusion that the claimed subject matter is adequately described are: (1) that the claim includes a structural limitation which limits the variability among species; and (2) that the specification provides an assay for identifying members of the genus that have the recited structural element (at least 95% identical to SEQ ID NO: 3) and the specified functional activity (catalyzing the reaction of A→B).

Both of the above-cited factors are found in the context of the present claims. First, all of the separin substrates included within the present claims must have a particular structural element, namely the amino acid sequence EXXR. This limitation substantially restricts the variability among species; *i.e.*, there are only 400 possible sequences having the EXXR motif. Second, the specification provides assays for determining if a given peptide having an EXXR sequence is capable of being cleaved by separin. For instance, Example 2 of the specification sets forth an *in vitro* assay for assessing Scc1 cleavage which can be used to test any putative substrate for its ability to be cleaved by separin. *See* specification at page 34, lines 16-26. The specification also sets forth a genetic screening assay using yeast cells that can readily identify nucleic acids that encode separin substrates. *See* specification at page 20, lines 6-12.

Thus, when the reasoning set forth in Example 14 of the USPTO's Written Description Guidelines is applied to the circumstances surrounding the currently presented claims, it must be concluded that the disclosed species are representative of the genus of EXXR peptide substrates, and therefore the written description requirement is fully satisfied.

Finally, the Examiner's attention is directed to the Federal Circuit's statement in *Regents of the University of California v. Eli Lilly & Co*:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

Id., 119 F.3d 1559, 1568 (Fed. Cir. 1997). Here, the generic formula "EXXR" indicates with specificity the genus of separin substrates encompassed by the claims. One skilled in the art can easily distinguish the formula EXXR from other formulae and can easily identify, not just "many," but *all* of the species (there are only 400) that are encompassed by this formula. Thus, according to the Federal Circuit's statement quoted above, the formula "EXXR" is an adequate description of the claimed genus.

The Examiner's basis for the written description rejection is that "[t]he genus [of separin substrates] is highly variable because a significant number of structural differences between genus members exists." *See* Office Action dated March 14, 2005, page 2. Applicants respectfully disagree. The claims specify that all members of the genus of separin substrates comprise an amino acid sequence EXXR. This represents a structural limitation that significantly limits the variability among species. Although the substrates may comprise additional amino acids (*e.g.*, amino acid sequences flanking the EXXR motif), the claims further limit the extent of structural variation among species by specifying that the substrate is capable of being cleaved by the separin. In view of the structural and functional

limitations in the claims, Applicants submit that the genus of separin substrates is not "highly variable," as asserted by the Examiner.

Finally, with respect to claim 58, Applicants note that this claim specifies that the substrate is human SCC1. The Examiner has included claim 58 in the written description rejection. The specification, however, provides working examples of the use of human SCC1 as a separin substrate. *See* Examples 10-13. It is unclear how human SCC1 can be regarded as being inadequately described when the specification provides explicit *working examples* which use human SCC1 as a separin substrate. Applicants respectfully suggest that the inclusion of claim 58 in the rejection was an inadvertent error since there is no legally justified basis for rejecting, under § 112, first paragraph, a claim that recites a particular species, when that exact species is disclosed in a working example in the originally filed specification.

In view of the foregoing, Applicants respectfully request that the rejection of claims 36, 37, 40, 41, 43, 44, 46-49 and 58 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

II. Claim Rejections Under 35 U.S.C. § 103

Claims 36, 37, 40, 41, 43, 44 and 48 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown *et al.*, *Analyt. Biochem. 217*:139-147 (1994) ("Brown") in view of Ciosk *et al.*, *Cell 93*:1067-1076 (1998) ("Ciosk"). *See* Office Action dated March 14, 2005, page 4. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify or combine the cited references. *See* M.P.E.P. § 2143.01. In addition, all of the claim limitations must be taught or suggested by the prior art. *See* M.P.E.P. § 2143.03. No evidence has been presented to indicate that a person of ordinary skill in the art would have been motivated to modify or combine Brown and/or Ciosk. In addition, not all of the elements of the currently presented claims are taught or suggested by Brown and/or Ciosk. Thus, a *prima facie* case of obviousness has not been established.

Brown refers to "a general radiometric assay for studying the proteolytic activities of endopeptidases using a tritiated-biotinylated peptide." *See* Brown, page 145, sentence bridging left and right columns. Brown illustrates the assay using cathepsin G, a synthetic substrate, and an inhibitor known as ACT. *See id.*, page 145, left column. According to Brown:

> Although specifically used here for an enzyme which cleaves at the N-terminus of BAP, this type of labeled peptide substrate is readily applied to the detection of other endoprotease activities, as well as inhibitors of these activities.

See id., page 147, middle left column. There is nothing in Brown, however, to suggest that the general assay mentioned therein could or should be adapted for use in identifying inhibitors of the proteolytic activity of separin.

The Examiner has relied on Ciosk for allegedly "teach[ing] a recombinant separin called Esp1p and its yeast substrate Scc1." *See* Office Action, page 4. There is nothing in Ciosk, however, to indicate that Scc1p is a proteolytic substrate of Esp1p. In fact, there is no suggestion whatsoever in Ciosk that Esp1p is a protease at all. Ciosk simply concludes that "Esp1p is required for both sister [chromatid] separation and dissociation of Scc1p from chromatin." *See* Ciosk, page 1070, bottom right column. Significantly, Ciosk suggests that whatever factor causes Scc1p to dissociate from chromatin is not necessarily responsible for its destruction. According to Ciosk, "Scc1p in yeast is indeed destroyed in an APC-dependent manner, but the timing of this event suggests that *it might be a consequence rather than a cause* of its dissociation from chromosomes." *See id.*, page 1073, middle right column (emphasis added). Thus, the conclusion in Ciosk that Esp1p causes Scc1p to dissociate from chromosomes would not suggest that Esp1p had any role in destroying Scc1p since it is noted that the destruction of Scc1p was believed to be a consequence, *not a cause*, of its dissociation from chromatin. A person of ordinary skill in the art, based on this reference, would therefore have had no reason to believe that Esp1p was involved in the destruction of Scc1p or that Esp1p is a protease.

As noted above, there is nothing in Ciosk to suggest that Esp1p is a protease. In terms of a proposed biological role for Esp1p, Ciosk states that:

> Esp1p might, for instance interact transiently with cohesins and facilitate their *dissociation* from chromosomes. Alternatively, it might destroy cohesion by an *indirect mechanism*, by *generating a global change within nuclei* that is more directly responsible for

> weakening sister chromatid cohesion. A candidate would be the concentration of Ca^{2+}, which appears to change at the metaphase to anaphase transition.

See Ciosk, page 1074, paragraph bridging left and right columns (emphasis added, internal citation omitted). Based on Ciosk, a person of ordinary skill in the art would have had no reason to believe that Esp1p is a protease, especially since Ciosk explicitly suggests that Esp1p may function by mechanisms such as altering the nuclear concentration of Ca^{2+}, a mechanism which does not in any way suggest a proteolytic role for this gene product.

In summary, nothing in Ciosk would have suggested that Esp1p is a protease or that Scc1p is in any way destroyed by Esp1p. Thus, a person of ordinary skill in the art, in view of Brown and Ciosk, would have had no motivation to include Esp1p and/or Scc1p in the proteolytic assay of Brown.

The Examiner has made specific reference to the *Experimental Procedures* section of Ciosk on page 1075. *See* Office Action, page 4. Nothing in this section of Ciosk, however, indicates that Scc1p is a proteolytic substrate of Esp1p.

Finally, in addition to the fact that Ciosk in no way suggests that Scc1p is proteolytically cleaved by Esp1p (or that Esp1p is a protease), Applicants further note that there is nothing in Ciosk (or Brown) to suggest the identification of test compounds that inhibit the proteolytic activity of a separin. In fact, there is nothing in Ciosk to even suggest the identification of compounds that influence the interaction between Esp1p and Scc1p (especially since Ciosk suggests that Esp1p's role in dissociating Scc1p from chromatin may

occur *indirectly*, *e.g.*, by causing global changes within the nucleus). An element of the currently claimed methods is "determining the inhibiting effect of the test compound on the proteolytic activity of the separin." Neither reference cited by the Examiner teaches or suggests this element. Thus, not all elements of the currently claimed methods are taught or suggested by the cited references. For this reason alone, a *prima facie* case of obviousness cannot be established.

Since a person of ordinary skill in the art would have had no motivation to modify or combine the cited references, and since not all elements of the currently claimed methods are taught or suggested by the cited references, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

III. Claim Objection

Claim 59 was objected to as being dependent upon a rejected base claim. *See* Office Action dated March 14, 2005, page 4. Claim 59 depends from claim 46, which in turn depends from claim 36. As discussed above, the rejections of claims 36 and 46 are in error and should be withdrawn. Accordingly, Applicants respectfully submit that the objection to claim 59 is also in error and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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